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| EXAMINER |
|---|
| SCHMIDT, MARY M |

| ART UNIT | PAPER NUMBER |
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| 1635 | 25 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/545,428 | LEVESQUE M D ET AL. | |
| | Examiner | Art Unit | |
| | Mary M. Schmidt | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,5,11,12,16 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,11,12,16 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Drawings*

1. The drawings filed 4-7-00 remain objected to as stated in the previous Official action mailed 11/20/2002, where a PTO-948 was provided, since the required corrections have not been made.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-2, 5, 8, 11-12, 16 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are now rejected over the breath of antisense to "a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product".

The specification as filed taught that MSX1 is an immediate early response gene involved in epidermal induction and inhibition of neuronal differentiation (page 3, lines 9-19); that HES1 is the hairy and enhancer of split homolog-1 (page 4, lines 21-31). The specification teaches on pages 13-14 the antisense to human MSX1 of SEQ ID NOS: 13 and 14 and the antisense to human HES1 of SEQ ID NOS:15 and 16. The GenBank Accession numbers are taught on page 14 for the human, *Ambystoma mexicanum* and chicken MSX1 gene and the human, rat, mouse, newt, yeast (*Saccharomyces pombe* and *Saccharomyces cerevisiae*) genes.

While the claims are considered to describe instant SEQ ID NOS:13-16 as the antisense to human MSX1 and HES1 for making the claimed transdifferentiated cells, these sequences are not considered to represent the breath of claimed "segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product".

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product

> claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

While the specification as filed teaches the Genbank sequences of human and other MSX1 and HES1 genes as summarized above, this teaching is not considered sufficient to describe the claimed genus of any non-human homologous counterpart as claimed. In order to design an antisense to a gene, the sequence of the gene must be known. The examples in the specification are not considered representative of antisense to any MSX1 or HES1 gene from any species since the examples in the specification are drawn only to human genes. Furthermore, it is not clear how antisense to any non-human homologous counterpart of MSX1 or HES1 would have a correlated function to allow for transdifferentiation of any type of epidermal basal cell into a cell expressing GFAP and/or O4. Absent further specific guidance by way of sequence structure, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of the breath of claimed MSX1 and/or HES1 genes from the genus of species claimed.

4. Claims 1-2, 5, 8, 11-12, 16 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using primary cells (with differentiated cells removed as in Example 1, page 25 of the specification) from human adult skin for transdifferentiation steps including administration of the human MSX1 (instant SEQ ID NOS: 13 and 14) and human HES1 antisense (instant SEQ ID NOS: 15 and 16) for making transdifferentiated cells having the physiological and/or immunological feature of a glial cell wherein said feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of those, does not reasonably provide enablement for the breath of methods and transdifferentiated cells claimed from any possible epidermal basal cell, and further, using antisense to MSX1 and HES1 from any species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to an *in vitro* method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

b) transferring said epidermal basal cell, in vitro, with one or more eukaryotic expression vector(s) containing at least one cDNA encoding a human neurogenic transcription factor, or

homologous non-human counterpart, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, such that at least one of the neurogenic transcription factor(s) is expressed in said cell;

c) growing the transfected cell in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these, in an amount sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product;

d) growing said epidermal cell with a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, sonic hedgehog aminoterminal peptide, and IK-6, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell; and

wherein the physiological and/or immunological feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein, and O4, or a combination of these.

Claim 2 is drawn to the method of claim 1, wherein the eukaryotic expression vector(s) of the transfection step comprise a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, and wherein the DNA encoding the neurogenic transcription factor is of human origin or is a homologous non-human counterpart.

Claim 5 is drawn to a trandifferentiated cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

an epidermal basal cell transfected with one or more eukaryotic expression vectors comprising a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor, or homologous non-human counterpart, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, wherein the DNA encoding the neurogenic transcription factor is of human origin, or is a non-human homologous counterpart, or is an active fragment of a gene encoding any of these, said cell being treated with at least one antisense oligonucleotide comprising a segment(s) of human MSX1 gene or human HES1 gene, or non-human homologous counterpart thereof, and wherein said cell was grown in the presence of a retinoid and at least one signal molecule selected from the group consisting of CNTF, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, thereby transdifferentiating said epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell said cell expressing at least one marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of these.

Claim 8 is drawn to a transdifferentiated cell produced by the process of claim 1.

Claim 11 is drawn to a kit for converting, in vitro, epidermal basal cells into cells having one or more morphological, physiological and/or immunological feature(S) of a glial cell, said kit comprising:

one or more eukaryotic expression vectors containing cDNA encoding a human neurogenic transcription factor, from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, or a non-human homologous counterpart of any of these;

at least one antisense oligonucleotide corresponding to the human MSX1 gene, the human HES1 gene, or a non-human homologous \ counterpart of either of these,

and a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, and sonic hedgehog aminoterminal peptide.

Claim 12 is drawn to the kit of claim 11 further comprising instructions for using (a), (b), and c) in transdifferentiating a mammalian subject's epidermal basal cell(s).

Claim 16 is drawn to the transdifferentiated cell of claim 8, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

Claim 22 is drawn to the transdifferentiated cell of claim 8 wherein the cell is of human origin.

Claim 23 is drawn to the cell of claim 8, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

Claim 24 is drawn to the transdifferentiated cell of claim 23, wherein the physiological and/or immunological feature is expression of glial fibrillary acidic protein (GFAP) or O4.

Claim 25 is drawn to an in vitro cell culture derived from the transdifferentiated cell of claim 8, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a glial cell.

Claim 26 is drawn to the method of claim 1, wherein culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s) comprises separating basal cells from keratinocytes using a calcium-free medium.

Claim 27 is drawn to the method of claim 1, wherein said antisense oligonucleotide(s) is modified with one or more thio groups.

The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to target human MSX1 (SEQ ID NOS: 13 and 14) and two antisense oligonucleotides to target human HES1 (SEQ ID NOS: 15 and 16). In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, filial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neurons. Table 1 teaches the results of the transdifferentiation experiments showing that a combination of neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression

was most effective at establishing transdifferentiation. The specification only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein, and would not appear to have the instantly claimed features of a glial cell. The specification does teach on page 31, lines 13-16 that a "small percentage (around 5%) of cells also express GFAP. This is an indication that transdifferentiated cells acquire characteristics of astroglial cells, either directly or indirectly." However, no further guidance as to which type of epidermal basal cells would differentiate into cells having GFAP and/or O4 markers, have been provided in the specification. Nor has any guidance been provided as to the breath of antisense to any species of MSX and/or HES that will provide the functions claimed of transdifferentiating the epidermal basal cells into cells having the GFAP and/or O4 markers.

As stated previously:

The textbook entitled "The Functional Roles of Glial Cells in Health and Disease", vol. 468 from the Advances in Experimental Medicine and Biology series, Ed. By Rebecca Matsas and Marco Tsacopoulos, Kluwer Academic/Plenum Publishers, New York, NY, 1999, teaches the following about glial cells in the preface: "Glial cells outnumber neurons and make up about one-half of the bulk of the nervous system. They are divided into two major classes: first, the macroglia, which include astrocytes and oligodendrocytes in the central nervous system, and the Schwann cells in the peripheral nervous system; and second, the microglial cells. These different classes of glial cells have different functions and contribute in different ways in the development,

function, and the pathology of the nervous system." The complexity of glial cell development, the discovered components of cell differentiation and development, and cell survival as a functioning glial cells are reviewed in chapter 1, Jessen et al., pages 3-10. It is stated on page 4, line 5, that "[l]ittle is known about the mechanisms that regulate the entry of crest cells to the glial lineage. One of the difficulties in studying this first step in PNS glial development has been the lack of a glial differentiation marker that defines an early lineage entry." They further state on page 4 that "[o]ne of the most notable features of the precursor cell is its acute dependence on axonal survival signals." On page 6, they state that "A striking feature of the Schwann cell phenotype is how unstable it is. If a nerve is an adult animal is transected, the myelinating and non-myelinating cells in the distal stump will promptly undergo radical lacerations in morphology and gene expression. The eventual outcome is the generation of an apparently single population of cells that show a state of differentiation comparable to that of immature cells prior to the formation of myelinating an non-myelinating cells....this process involves the dedifferentiation or development regression of individual Schwann cells and myelin break-down." These teachings provide the complexity in the art for the types of glial cells, their functions, and their carefully regulated cell phenotypes.

While the textbook, Developmental Biology, 5th Ed. , Scott F. Gilbert, Sinauer Associates, Inc. Pub., Sunderland, Mass., 1997, pages 297-299, taught in Figure 7.42, the "Hypothetical lineage restriction in the cells of the quail cephalic neural crest", the potential for glial cell development to take many different paths is clear. Neither the prior art nor the

specification as filed taught the clearly delineated pathology of development of any type of glial cell from epidermal basal cells. As such, it is not taught in either the prior art or the instant specification as filed what types of epidermal basal cells may be useful to transdifferentiate into cells having the GFAP and/or O4 marker, and further what types of MSX and/or HES antisense from any other species are able to cause such transdifferentiation of any possible epidermal basal cells from any organism.

MPEP 2164 teaches the following standards for a determination of whether the specification taught how to make and use the claimed invention at the time the invention was made by weighing whether or not undue experimentation was required to make and use the invention as claimed. MPEP 2164.01(a) lists the factors for determining "whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) the amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)"

The level of unpredictability in the field of development of glial cells from epidermal basal cells was high. One of skill in the art could not predict whether or not cells having GFAP and/or O4 markers could be produced from epidermal basal cells in cell culture. Nor could one

of skill in the art predict whether or not cells having GFAP and/or O4 markers could be made from any type of epidermal basal cells from any organism using the methods disclosed in the instant specification as filed. Absent more specific guidance in the art for which specific cell populations may be used and which antisense must be expressed in the such epidermal basal cells, one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breath of claimed transdifferentiated glial cells and methods of making said cells.

5. Claims 1, 2, 5, 8, 11, 12, 16, 22-27 are free of the prior art since the prior art did not teach nor fairly suggest the claimed step of use of antisense to MSX1 and HES1 found in each of the instant method and composition claims.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

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M. M. Schmidt
May 28, 2003